REMARKS

Claims 171-184 are pending and under consider in the present application. Claims 185-192 have been added. Claims 171 and 178 have been amended. Claims 144-156 have been cancelled, without prejudice.

No new matter has been added with the amendments and newly added claims. The amendments to claims 171 and 178 regarding a eukaryotic cell is supported for example by page 3, lines 21-23. Newly added claims 185, 188, and 191, which recite a membrane impermeant substrate that is transformed by the cell into a membrane permeant substrate, are supported for example by page 4, lines 16-19. Newly added claims 186, 189, and 191, which recite using FACS, are supported for example, by page 45 lines 8-10. Newly added claims 187, 190, and 191, which recite a 1.5-fold change in beta lactamase expression, are supported by the disclosure for example at Table 3 on page 63, which indicates various levels of change of beta-lactamase expression, including a 1.5-fold induction. Upon entry of the present amendment, claims 171-192 will be pending and under consideration.

Priority

The Office Action alleges that neither PCT application PCT/US97/17395 nor U.S. App. No. 08/719,697, priority documents of the present invention, provide adequate support for the claimed invention. Therefore, priority was not granted for the pending claims to these applications. The Applicants respectfully traverse this determination. The Office Action asserts that there is no support in the priority applications for the requirement that the clonal cells exhibit a 1.5 fold change in beta-lactamase expression. Furthermore, the Office Action alleges that the priority applications lack support for the concept of a "cell sensor panel." Therefore, the pending claims were not granted the priority date of the priority applications.

The earliest priority application in the chain of priority applications of the present application is U.S. App. No. 08/719,697, which was filed on September 26, 1996. Although this application does not specifically mention the term "cell sensor panel," the application adequately discloses cell sensor panels in discussing, for example, a method of functionally characterizing a

target using a panel of clones (U.S. App. No. 08/719,697, page 28, lines 14 to 28), a method of test compound profiling using a panel of clones (U.S. App. No. 08/719,697 page 28, line 29 to page 29, line 4), and a library of clones for screening a target or a modulator of the target (U.S. App. No. 08/719,697, page 27, line 26 to page 28, line 5). Regarding the phrase "at least a 1.5 fold change in beta-lactamase expression," independent claims 171 and 178 as amended do not recite this phrase. However, newly added claims 187, 190, and 191, recite this phrase. "At least a 1.5 fold change in beta-lactamase expression" is supported by U.S. App. No. 08/719,697, for example at Table 3 on page 41, which indicates that one of the clones, R2, exhibited a 1.5-fold induction upon stimulation with ionomycin. Other elements of the pending claims are supported by the disclosure of U.S. App. No. 08/719,697, as well. For example, page 21, lines 17-19, disclose that viral vectors can be used for integration of beta-lactamase into a genome. Therefore, the pending claims are supported by the disclosure of U.S. App. No. 08/719,697, and Applicants respectfully request that the Examiner grant the pending claims the priority date of this Application, September 26, 1996.

Rejection Under 35 U.S.C. § 112, Second Paragraph

The Applicants respectfully traverse the rejection of claims 171-177 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Office Action alleges that there is insufficient antecedent basis in claim 177 for the term "said target" in line 6. Claim 177 as amended recites "a target." Therefore, the rejection has been overcome. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

Rejection Under 35 U.S.C. § 103

Applicants respectfully traverse the rejection of claims 171-184 under 35 U.S.C. § 103 as being unpatentable over Forrester et al. (*Proc. Natl. Acad. Sci.* 93:1677 (1996) in view of Tsien et al. (WO 96/30540) and further in view Hicks et al. (*Meth. Enzymol.* 254:263 (1995)). The

Office Action asserts that Forrester et al. teach a plurality of clonal cells wherein each clonal cell includes a distinct fusion RNA of a cellular RNA transcript and a beta-galactosidase polynucleotide. Furthermore, the Office Action asserts that the clonal cells of Forrester et al. exhibit as much as a 12.4-fold induction in beta-galactosidase expression in response to the induction of expression of the target in the clonal cells after exposure of the clonal cells to a ligand for the target.

The Office Action acknowledges that Forrester et al. do not teach the use of beta-lactamase in place of Beta-galactosidase as the reporter. Furthermore, the Office Action indicates that it is unclear whether the vector of Forrester is a viral vector. However, the Office Action asserts that Tsien et al. teaches the use of beta-lactamase in place of beta-galactosidase. Furthermore, the Office Action asserts that Hicks teaches the use of a retroviral gene trap vector.

Regarding combining Tsien et al. with Forrester et al., the Office Action asserts that it would have been obvious to modify the method of Forrester et al. to substitute the B-lactamase enzyme of Tsien et al. for beta-galactosidase, since Tsien et al. allegedly teaches that use of the novel beta-lactamase substrates provides distinct advantages over use of substrates for known reporter genes including beta-galactosidase because of the high efficiency, diffusion control, sensitivity, and detection within living cells of the beta-lactamase substrate. Regarding combining Hicks et al. with Forrester et al., the Office Action cites statements in Hicks indicating that retrovirus vectors are easier to use, especially for large scale mutagenesis, and the structure of the recombinant product is more predictable.

In order to be relied upon in an obvious rejection, cited art must be prior art under 35 U.S.C. § 102. MPEP § 2141.01. To establish a prima facie case of obviousness there must be some suggestion or motivation in the prior art to make the claimed invention, there must be a reasonable expectation of success, and the prior art reference must teach or suggest all of the claim limitations. MPEP § 2142; In re Vaeck, 947 F.2d 488, 20 USPQ2d, 1438 (Fed. Cir. 1991). The patent office has the burden of establishing a prima facie case of obviousness. Id. The teaching or suggestion to make the claimed combination must be found in the prior art and not

based on the Applicants' disclosure. MPEP § 706.02 citing In re Vaeck, 947 F.2d 488 (Fed. Cir. 1991); MPEP § 2145, section XD.

As discussed above, the pending claims are supported by the disclosure of parent application U.S. App. No. 08/719,697, filed September 26, 1996. The Office Action relied on Tsien et al. (PCT WO 96/30540) for the teaching of the use of beta-lactamase as the reporter gene in the presently claimed invention. However, Tsien et al. was published October 3, 1996, after the September 26, 1996 filing date of U.S. App. No. 08/719,697. Therefore, Tsien et al. is not prior art under 35 U.S.C. § 102, and accordingly cannot be relied upon in an obviousness rejection under 35 U.S.C. § 103 (MPEP § 2141.01).

Furthermore, even if Tsien et al. could be relied upon as prior art, and Applicants reassert that it cannot, there is no teaching or suggestion to combine Tsien et al. with Forrester et al. and Hicks et al. As discussed above, the Office Action asserts that Tsien et. al. suggests the combination in allegedly teaching that the use of the novel beta-lactamase substrate compounds provide distinct advantages over known reporter genes including beta-galactosidase because of the high efficiency, diffusion control, sensitivity, and detection within living cells of the beta-lactamase substrate. However, none of these "advantages" would suggest combining Tsien et al. and Forrester et al. to a person of ordinary skill in the art because there is no indication in Forrester et al. of the need in their gene trap screen method for a reporter that provides these "advantages." Furthermore, there is no indication in Tsien et al. that substrates disclosed therein would be advantageous in gene trap assays.

The present application discusses the important advantages related to the pending claimed invention, of using beta-lactamase over prior technologies such as those utilizing beta-galactosidase. These advantages include the ability to functionally screen immediately after the rapid identification of a functionally active portion of a genome without the necessity of transferring the identified portion of the genome into a secondary screening system and without the need to attempt to identify and grow clone stocks (Page 17, lines 8-15). Figure 1 of the present application diagrammatically illustrates this advantages of the present invention over prior art references that involve beta-galactosidase. These advantages of using beta-lactamase

substrates is not taught or mentioned in Forrester et al., Tsien et al., or Hicks et al. Furthermore, the cited references are silent as to issues related to permeabilization of cells when using beta-galactosidase to detect expression in single cells (Page 42, lines 1-3). In fact, Forrester et al. utilize a freeze/thaw cycle to release beta-galactosidase for quantitative assay (Forrester et al., page 1677, right column, 4th full paragraph), which could affect the accuracy of assay results. By utilizing a beta-lactamase system, the present invention provides for the detection of reporter gene expression without the need to permeabilize cell.

Since the teaching or suggestion to make the claimed combination is based on the Applicants' disclosure and not on the cited prior art references, the Applicants respectfully assert that these references do not render the invention of the pending claims obvious. Accordingly Applicants respectfully request withdrawal of the rejection of claims 171-184 under 35 U.S.C. § 103 as being unpatentable over Forrester et al. (*Proc. Natl. Acad. Sci.* 93:1677 (1996) in view of Tsien et al. (WO 96/30540) and further in view Hicks et al. (*Meth. Enzymol.* 254:263 (1995)).

CONCLUSION

In view of the amendments and the above remarks, it is submitted that the application is in condition for allowance and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this application.

Please charge any additional fees, or make any credits, to Deposit Account No. 50 1355

Respectfully submitted,

Date: June 30, 2003

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